REMARKS

This paper is filed in response to the Final Office Action mailed February 22, 2010. Claims 1 to 11 are pending and claims 1 to 8 and 10 are under consideration.

I. REJECTIONS UNDER 35 U.S.C. §103(a)

The rejection of claims 1 to 4, 6 to 8 and 10 under 35 U.S.C. §103(a) as allegedly obvious over Nojiri *et al.* (J. Biochem. 125:696 (1999)) is respectfully traversed. Allegedly, Nojiri *et al.* teach or suggest each and every element claimed, as set forth on pages 2 to 4 of the Office Action.

Applicants respectfully point out that in order to establish obviousness under 35 U.S.C. §103(a), there must have been a suggestion or motivation to modify the reference; a reasonable expectation of success of producing the claimed invention; and the reference must teach or suggest each and every claim limitation. Both the teaching or suggestion to modify the reference *and* the reasonable expectation of success *must both be found in the prior art, not in Applicants' disclosure*. See, e.g., *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991) and *In re O'Farrell*, 853 F.2d 894, 903-904 (Fed. Cir. 1988) (*emphasis added*).

Firstly, Nojiri *et al.*, at best, describe a plasmid system in which α and β subunit genes are expressed on the same plasmid (see, for example, page 700, second column, third paragraph). In particular, the nucleic acid sequences encoding α subunit of the nitrile hydratase and β subunit of the nitrile hydratase are on the same plasmid, and not on different plasmids. Here, in contrast to Nojiri *et al.*, the claims recite that the nucleic acid sequences encoding the α subunit of the nitrile hydratase and the β subunit of the nitrile hydratase are each present separately on the first and second plasmids, and not on the same plasmid.

In fact, Nojiri *et al.* fail to describe, at all, an expression system in which the nucleic acid sequences encoding the α subunit of the nitrile hydratase and the β subunit of the nitrile hydratase are each present separately on the first and second plasmids, and not on the same plasmid. Furthermore, there is no suggestion whatsoever in Nojiri *et al.* to produce an expression system in which the nucleic acid sequences encoding the α subunit of the nitrile hydratase and the β subunit of the nitrile hydratase are each present separately on the first and second plasmids, and not on the same plasmid. In this regard, Nojiri *et al.* state that in a system in which the α subunit of the nitrile hydratase and the β subunit of the nitrile hydratase are on the same plasmid that "the amounts of the α and β subunit expressed were

not equal...expression of the β subunit was fairly low compared with that of the α subunit." (page 701, first column, second paragraph) In order to increase expression of the β subunit, Nojiri *et al.* add a second plasmid expressing a β subunit (pHSGβ) to the plasmid expressing both the α and β subunits. (page 701, first column, third paragraph) Thus, Nojiri *et al.* fail to teach or suggest modifying this system such that the nucleic acids encoding the α subunit of the nitrile hydratase and the β subunit of the nitrile hydratase are each present separately on the first and second plasmids, and not on the same plasmid.

Moreover, Nojiri *et al.* fail to provide any motivation to produce the claimed expression system, as the authors state that "We have succeeded in producing a large amount of a functional NHase in *E. coli* by optimizing the cultivation conditions and co-expressing the NHase activator encoded downstream of the β subunit gene." (page 697, first column, third paragraph) In view of the fact that Nojiri *et al.* state that the system they developed produced a large amount of functional NHase, why would one of skill in the art at the time of the invention have had any motivation to further modify the expression system of Nojiri *et al.* at all, let alone a motivation to develop an expression system in which the nucleic acid sequences encoding the α subunit of the nitrile hydratase and the β subunit of the nitrile hydratase are each present separately on the first and second plasmids, and not on the same plasmid? In this regard, the Examiner provides no explanation, but merely concludes a motivation somehow would have existed. Absent such a motivation, one skilled in the art would have no reason to develop an expression system in which the nucleic acid sequences encoding the α subunit of the nitrile hydratase and the β subunit of the nitrile hydratase are each present separately on the first and second plasmids, and not on the same plasmid.

Secondly, not only does Nojiri *et al.* fail to teach or suggest the claimed expression system, namely an expression system in which the nucleic acid sequences encoding the α subunit of the nitrile hydratase and the β subunit of the nitrile hydratase are each present separately on first and second plasmids, and not on the same plasmid, the specification discloses that the claimed expression system provides unexpected results. Particularly, the specification discloses that nitrile hydratase activity was increased more than eight times: "In this connection, it may be particularly surprising that simply expressing the nucleic acid sequences encoding the corresponding nitrile hydratase subunits, which nucleic acid sequences are in fact organized in one operon, separately on different plasmids contributes to increasing the activity of the resulting nitrile hydratases by a factor of >8 as compared with

the 'normal' expression."(Specification, page 5, lines 29 to 37). The fact that expression on separate plasmids led to increased nitrile hydratase activity is unexpected in view of the cited references, and as such, is evidence of non-obviousness.

Thirdly, with respect to the statement in the Office Action that "one of skill in the art would have been motivated to separate the alpha and beta subunits in order to get better NHase activity and increased production of the beta subunit," (Office Action, page 5) Applicants respectfully disagree. If anything, this position would be counterintuitive to one of skill in the art at the time of the invention. In particular, expressing the α subunit of the nitrile hydratase and the β subunit of the nitrile hydratase on separate plasmids would entail modifying the Nojiri *et al.* expression system to delete the β subunit from the plasmid that also contained the α subunit and β subunit together. However, the Examiner fails to explain why or how deleting the β subunit from the plasmid containing both α and β subunits would have been expected by one of skill in the art to result in *increased* β subunit production since doing so results in fewer copies of the β subunit gene being available for expression. Moreover, why would one of skill in the art have even been motivated to do so? To the contrary, one of skill in the art at the time of the invention would not have been motivated to do so because they would have expected that deleting the β subunit gene from the plasmid with the α subunit would lead to *decreased* β subunit production, not increased β subunit expression. As such, one skilled in the art would not have been motivated to remove the β subunit from the plasmid containing both α and β subunits to *increase* β subunit expression, since doing so would result in decreased β subunit expression, precisely the opposite effect desired. Hence, the Patent Office's position to delete a β subunit from the same plasmid as the α subunit in order to increase production of the β subunit is clearly scientifically untenable. Consequently, for at least these reasons, one of skill in the art would not have had a motivation to modify the Nojiri *et al.* expression system to delete the β subunit gene from the plasmid with the α subunit in order to produce an expression system in which the nucleic acid sequences encoding the α subunit of the nitrile hydratase and the β subunit of the nitrile hydratase are each present separately on the first and second plasmids, and not on the same plasmid.

In sum, Nojiri *et al.* fail to teach or suggest, nor would have motivated one of skill in the art at the time of the invention to develop an expression system of claims1 to 4, 6 to 8 and 10. Consequently, claims1 to 4, 6 to 8 and 10 would not have been obvious in view of Nojiri

et al. (J. Biochem. 125:696 (1999)) under 35 U.S.C. §103(a) and the rejection must be withdrawn.

The rejection of claim 5 under 35 U.S.C.§103(a) as allegedly obvious over Nojiri *et al.* (J. Biochem. 125:696 (1999)) in view of Nishiyama *et al.* (J. Bacteriol. 173:2465 (1991)) is respectfully traversed. Allegedly, Nojiri *et al.* in combination with Nishiyama *et al.* teach or suggest each and every element claimed, as set forth on pages 4-5 of the Office Action.

Nishiyama *et al.* (J. Bacteriol. 173:2465 (1991)) fail to provide that which is missing from Nojiri *et al.* Namely, Nishiyama *et al.* fail to teach or suggest, or provide any motivation to develop an expression system in which the nucleic acid sequences encoding the α subunit of the nitrile hydratase and the β subunit of the nitrile hydratase are each present separately on the first and second plasmids, and not on the same plasmid. Consequently, at the time of the invention one of skill in the art, in view of Nojiri *et al.* alone, or in combination with Nishiyama *et al.*, would not have had a motivation to develop an expression system different from Nojiri *et al.*, let alone a system in which the nucleic acid sequences encoding the α subunit of the nitrile hydratase and the β subunit of the nitrile hydratase are each present separately on the first and second plasmids, and not on the same plasmid.

In sum, Nojiri *et al.* and Nishiyama *et al.* alone, or in combination, fail to teach or suggest, or would have motivated one of skill in the art at the time of the invention to develop an expression system of claim 5. Consequently, claim 5 would not have been obvious in view of Nojiri *et al.* (J. Biochem. 125:696 (1999)) and Nishiyama *et al.* (J. Bacteriol. 173:2465 (1991)) under 35 U.S.C. §103(a) and the rejection must be withdrawn.

CONCLUSION

In summary, for the reasons set forth herein, Applicants maintain that the claims clearly and patentably define the invention, respectfully request that the Examiner reconsider the various grounds set forth in the Office Action, and respectfully request the allowance of the claims which are now pending.

If the Examiner would like to discuss any of the issues raised in the Office Action, Applicant's representative can be reached at (858) 509-4065. Please charge any fees associated with the submission of this paper to Deposit Account Number 033975. The Commissioner for Patents is also authorized to credit any over payments to the above-referenced Deposit Account.

Respectfully submitted,

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